"What some call health, if purchased by perpetual anxiety about diet, isn't much better than tedious disease."

—George Dennison Prentice

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Nutrition Close-Up is a quarterly publication for the Canadian Egg Marketing Agency, written and produced by the Egg Nutrition Center. *Nutrition Close-Up* presents up-to-date reviews, summaries and commentaries on the latest research on the role of diet in health promotion and disease prevention, including the contributions of eggs to a nutritious and healthful diet.

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Egg Consumption, Lifestyle Factors, and All-Cause Mortality in the Physicians' Health Study I

In 1968, the American Heart Association advised patients with high blood cholesterol to limit their dietary cholesterol intake to 300 mg/day. In 1995, this advice entered the official US dietary guidelines as a recommendation for the general public. Since that time, US dietary recommendations have continued to limit cholesterol intake to 300 mg/day. Although eggs are an important contributor of dietary cholesterol, an association between egg intake and heart disease has not been established. In fact, studies that have controlled for sources of dietary saturated fat (such as bacon and butter) have concluded that egg intake is not independently associated with CVD risk (suggesting that it's not the eggs, but the company they keep). Furthermore, existing research on dietary cholesterol and CVD risk has yielded inconsistent results. To further investigate the relationship between egg intake and the risk of CVD (and mortality), Djoussé and Gaziano evaluated data from the Physicians' Health Study I, a long-term prospective cohort trial including information from 21,327 participants.

...the physicians in this study who reported the most frequent egg consumption were also more likely to be current smokers, overweight, less physically active, diabetic, hypercholesterolemic, and hypertensive, all of which might indicate non-compliance with current health recommendations.

The original Physicians' Health Study I was designed to evaluate low-dose aspirin and beta carotene for the prevention of CVD and cancer. Participants completed an abbreviated semi-quantitative food-frequency questionnaire at baseline and every two years thereafter until the study concluded. They were asked to report their average egg intake for the previous year. Response categories included: rarely or never, 1-3 times/month, 1 time/week, 2-4 times/week, 5-6 times/week, daily, and >2 times/day. Fruit, vegetable, and breakfast cereal intake was also obtained from each participant at baseline, as well as information on physical activity, smoking, alcohol consumption, parental history of premature myocardial infarction (MI), and history of hypercholesterolemia.

Data from a total of 21,327 physicians were available for analysis. After 20 years of follow-up, there were 1,550 new MIs, 1,342 strokes, and 5,169 deaths within this study cohort. Egg consumption was not associated with MI, total stroke, or type of stroke (ischemic or hemorrhagic). While the consumption of up to 6 eggs/week was not associated with any endpoint, consumption of 7 or more eggs per week was associated with a modest, but statis-

Continued on page 2

tically significant 23% increase in the risk of all-cause mortality after controlling for potential confounders. This association was stronger among participants with diabetes. Hypercholesterolemia status at baseline did not appear to influence the association between egg intake and the risk of CVD or mortality. Comparing the lowest with the highest categories of egg consumption, intake of ≥7 eggs per week was associated with a 22% increased risk of all-cause mortality among non-diabetic participants. For diabetic participants, the risk doubled (P for interaction between diabetes and egg consumption = 0.029 in the parsimonious model and 0.09 in the multivariate-adjusted model.)

Median egg consumption in this cohort was 1 per week. Higher egg consumption was associated with older age, higher body mass index (BMI), smoking, alcohol consumption, higher vegetable intake, less frequent consumption of breakfast cereal, use of multivitamins, presence of diabetes and hypertension, hypercholesterolemia, less physical activity, and parental history of premature CAD.

In this study, there was no increase in risk of CVD or all-cause mortality for healthy US male physicians consuming up to 6 eggs per week. Consumption of 7 or more eggs per week was associated with an increased risk of all-cause mortality, but not with MI or stroke. This is an unusual finding in light of the data from several other large cohort studies, none of which have found any association between egg consumption and CVD, stroke, or mortality. The link between high egg intake and increased all-cause mortality in diabetic men, however, supports the findings of several other recent studies, underscoring the importance of clarifying this relationship and uncovering possible mechanisms. It is important to note that the physicians in this study who reported the most frequent egg consumption were also more likely to be current smokers, overweight, less physically active, diabetic, hypercholesterolemic, and hypertensive, all of which might indicate non-compliance with current health recommendations. None of the studies to date showing a relationship between high egg intake and CVD or mortality in diabetic participants have included measures of metabolic control, a potentially confounding factor given the associated lifestyle factors. Further research in this area is warranted in light of these findings. ■

Djoussé L and Gaziano JM. Egg consumption in relation to cardiovascular disease and mortality: the Physicians' Health Study. *Am J Clin Nutr* 2008;87:964-9.

KEY MESSAGES

- In this study, there was no increase in risk of CVD or all-cause mortality for healthy US male physicians consuming up to 6 eggs per week.
- Consumption of 7 or more eggs per week was associated with an increased risk of all-cause mortality, but not with MI or stroke.
- The association between high egg intake and all-cause mortality in diabetic male physicians is not well understood and warrants further research.
- The physicians in this study who reported the most frequent egg consumption were also more likely to be current smokers, overweight, less physically active, diabetic, hypercholesterolemic, and hypertensive, all of which might indicate non-compliance with current health recommendations.

Special Feature:
Egg Nutrition Research Presented at Experimental Biology 2008

Effects of increased dietary protein and meal patterning on appetite during short-term energy balance and energy restriction

Objective: This study assessed whether the timing of increased dietary protein intake throughout the day influences the feeling of fullness during energy balance (EB) and restriction (ER).

Methods: Nine men (age: 45±5 y; BMI: 32.5±0.6 kg/m^2) randomly completed 5 controlled feeding trials consisting of 3 days each of EB and ER (750 kcal/d reduction).

The diet was composed of a normal amount of protein (NP) (0.8 g protein/kg^{-1}/d^{-1}) or an additional amount of protein (HP) (+0.6 g protein/kg^{-1}/d^{-1}) given at breakfast (B), lunch (L), dinner (D), or equally divided among all meals (E). Feelings of fullness were assessed over 15 h.

Results: No difference in fullness was observed between the EB vs. ER trials; thus, the data were combined. With all HP meals combined, HP led to higher fullness (P<0.05) across the day vs. NP. When comparing the timing of increased protein intake, the 3-h postprandial, subsequent meal, evening, and overall fullness were not different between HP-L, HP-D, or HP-E vs. NP but were higher for HP-B vs. NP (P<0.05 for all effects except evening (P=0.1). Comparing the HP treatments, the HP-B led to greater overall fullness vs. HP-L (P<0.005) and HP-D (P<0.01) but not for HP-E.

Conclusion: Increased dietary protein provided at breakfast leads to immediate and sustained increases in feelings of fullness in overweight men.

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Plasma concentrations of lutein and zeaxanthin are increased by egg intake during a carbohydrate restricted weight loss intervention

Methods: Twenty eight men (BMI 26-37 kg/m^2) were instructed to consume a carbohydrate restricted diet for 12 wk. Subjects were randomly allocated to consume either 3 eggs (EGG) per day (600 additional µg of lutein + zeaxanthin) or the equivalent of egg substitute (SUB) (0 additional µg of lutein + zeaxanthin).

Results: After 12 wk, subjects in the EGG group had higher plasma HDL cholesterol and larger HDL particles compared to those in the SUB group (P<0.001). Dietary intake of lutein and zeaxanthin was similar between groups, but subjects in the EGG group had a significant increase in plasma lutein (0.544±0.245 µmol/L at baseline to 0.929±0.420 µmol/L after 12 wk) compared to the SUB group (0.5269 µmol/L at baseline to 0.5269±0.348 µmol/L after 12 wk) (P<0.0001). A significant 46% increase in plasma zeaxanthin (P<0.025) was observed for the EGG group while there were no changes for the SUB group. There were no differences in dietary intake or plasma concentrations of beta-carotene, alpha carotene and beta-cryptoxanthin between groups. However, dietary intake of lycopene (P<0.05) was reduced between baseline and 12 wk for both groups and these reductions were associated with a significant reduction in plasma lycopene (P<0.01).

Conclusion: These results indicate that self-selected carbohydrate restricted diets are associated with adequate ditary intake of carotenoids with the exception of a reduced intake of lycopene. These data also suggest that the matrix of the egg makes for a better absorption of lutein and zeaxanthin and that the increased HDL size in the EGG group may contribute to the higher concentration of these carotenoids in circulation

Vaishnav U, Mutungi G, Waters D, Clar RM, Volek JS, Fernandez ML. Nutritional Sciences, Kinesiology, University of Connectictu, Storrs, CT. Research supported by a grant from the American Egg Board.

Eggs Enhance Anti-Inflammatory Effects of Carbohydrate-Restricted Diets

Chronic inflammation is one of the best-known independent predictors of cardiovascular disease and has been shown to promote both insulin resistance and atherosclerosis. Although research is clarifying the role of diet in modulating inflammatory processes in the body, there is still much to learn. Studies indicate that dietary carbohydrate plays a role in the initiation of several pro-inflammatory processes. Indeed, high-carbohydrate diets have been associated with increased biochemical markers of inflammation. Recent data from Mutungi et al. have demonstrated that a restricted-carbohydrate diet regimen that incorporated 3 eggs per day raised HDL levels and improved metabolic syndrome indices in overweight men. (The men who were assigned to consume an egg substitute as part of the carbohydrate-restricted regimen experienced no improvement in HDL cholesterol levels). Eggs provide many vital nutrients, including high-quality protein, choline, vitamin D, vitamin B_{12}, and iron. Eggs also provide a highly bioavailable form of lutein, an important antioxidant thought to mitigate certain inflammatory processes. To determine whether the inclusion of eggs in a carbohydrate-restricted diet would modulate inflammatory markers, the same group of researchers analyzed dietary and biochemical data from the original study.

In a randomized, single-blinded, placebo-controlled study, researchers from the University of Connecticut at Storrs sought to answer this question. Twenty-eight overweight/obese (BMI 26-37 kg/m²) men aged 40-70 years were recruited to participate in a 12-week diet trial that would evaluate the results of adding 3 eggs per day to a CR diet. All participants were asked to consume CR diets (consisting of 10-15% of energy from carbohydrate, 25-30% from protein, and 55-60% from fat) for the duration of the study. Each participant was randomly assigned to consume 3 eggs (providing 640 mg/d additional dietary cholesterol, 1.8 g carbohydrate, 19 g protein, 23 g fat, and 1239 kJ) or an equivalent volume of fat-free, cholesterol-free egg substitute (providing 2.9 g carbohydrate, 19.8 g protein, 0.3 g fat, and 394 kJ) each day of the study. The egg substitute had the same color and consistency as the liquid whole eggs provided by research coordinators.

Diet records and 12-hour fasting blood samples were collected at baseline, week 6, and week 12. In addition to serum lipids, several serum inflammatory markers were measured, including C-reactive protein (CRP), TNF-alpha, MCP-1, VCAM-1, and ICAM-1. Adiponectin, an anti-inflammatory and anti-atherogenic hormone, was also measured. Body composition (measured by dual-energy x-ray absorptiometry [DXA]), blood pressure, and anthropometrics were also measured at these time points. Participants were also asked to maintain their normal activity level throughout the study and provided records of their physical activity at baseline and once each week for the duration of the study. Participants were free-living and were not counseled to limit energy intake.

The eggs and egg substitute were the only foods provided by the study coordinators. Participants received dietary counseling from registered dietitians and were provided with detailed instructions for each dietary intervention, including goals, lists of appropriate foods (meat, fish, vegetables, some cheese, small amounts of seeds and nuts, low-carbohydrate salad dressing), recipes, sample meal plans, and food record sheets. Participants were instructed not to consume eggs outside of the eggs or egg substitute provided to them by the study coordinators. Compliance was evaluated during weekly follow-up visits.

Dietary analysis showed that by week 12, calorie consumption dropped significantly from baseline for both groups ($P<0.05$). Carbohydrate consumption also decreased from baseline for participants in both groups (from 42% of calories at baseline to 17% of calories by week 12; $P<0.001$). By week 12, participants in the EGG group had reduced their carbohydrate intake to 14.9% from 42.4% (at baseline), while SUB group participants reduced their carbohydrate intake to 19.1% from 41.5% at baseline. Participants in both groups increased their protein intake (from 17.8% at baseline to 25.8% at week 12; $P<0.001$) and fat intake (from 39.6% at baseline to 55.6% at week 12; $P<0.001$. Dietary cholesterol intake differed between groups, as intended. The EGG group increased their cholesterol consumption from 319±150 mg/day (baseline) to 827±192 mg/d ($P<0.0001$).

While adiponectin levels rose significantly in both groups ($P<0.01$), the increase was greater in the EGG group (15.3 g/L to 18.5 g/L) ($P<0.05$). CRP values were significantly reduced in the EGG group (from 5.95 mg/L to 4.33 mg/L, while the SUB group experienced only a non-significant decrease in CRP. Neither ICAM-1, nor VCAM-1 levels changed from baseline in either group. Following the 12-week intervention, fasting MCP-1 levels were significantly lower for the SUB group ($P<0.05$), but remained unchanged for the EGG group. No changes were observed in either group for TNF-alpha or IL-8 levels.

Body weight, BMI, percent body fat, waist circumference, and systolic and diastolic blood pressure decreased similarly from baseline for all participants, regardless of group assignment.

Abdominal adiposity also decreased similarly for both groups. Total cholesterol, LDL cholesterol, and the LDL:HDL cholesterol ratio remained unchanged over the course of the study for participants in the EGG and SUB groups. TAG levels decreased by 45% for participants in both groups ($P<0.0001$). Participants in the EGG group saw increases in HDL cholesterol (from 1.23±0.39 mmol/L [47.6±5.1 mg/dL] at baseline to 1.47±0.39 mmol/L [57.1±15.1 mg/dL] at week 12; $P<0.001$). HDL cholesterol remained unchanged for participants in the SUB group. Out of the 15 EGG group participants, 13 experienced increases in their HDL concentrations following the 12-week intervention. Increased HDL levels were observed in only 3 of the 13 participants in the SUB group. Plasma insulin levels decreased significantly from baseline in both groups. Plasma lutein increased in the EGG group from 0.54±0.24 µmol/L to 0.93±0.42 µmol/L ($P<0.01$), but remained unchanged in the SUB group.

These data indicate that carbohydrate-restricted diets help curb inflammation, as evidenced by the increase in adiponectin in both study groups. Among those participants consuming whole eggs as part of the CR regimen, the researchers observed a greater increase in adiponectin and a significant decrease in CRP levels. The authors note that this finding could be due, in part, to the biologically available lutein found in egg yolk. Including eggs in carbohydrate restricted diets appears to improve inflammatory markers in overweight men. At baseline, 18 (58% of total) participants were classified as having the metabolic syndrome. Of these, 11 were randomized to the EGG group and 7 to the SUB group. By the conclusion of the study, only 3 (all in the SUB group) still met the criteria for the metabolic syndrome. Overall, these findings demonstrate that CR diets can help reduce risk factors in overweight/obese men who meet the criteria for the metabolic syndrome and that eggs might be an ideal source of protein for use in such diets, given the improvements in inflammatory markers and HDL cholesterol levels among participants consuming whole eggs. ■

Mutungi G, Ratliff J, Fernandez ML, et al. Dietary cholesterol from eggs increases plasma HDL cholesterol in overweight men consuming a carbohydrate-restricted diet. *J Nutr* 2008;138(2):272-6.

Ratliff JC, Mutungi G, Puglisi MJ, Volek JS, Fernandez ML. Eggs modulate the inflammatory response to carbohydrate restricted diets in overweight men. *Nutrition and Metabolism* 2008;5:6.

Choline Intake and Breast Cancer Risk

Researchers have observed an association between dietary methyl donors and cancer risk in several studies, but the relationship remains unclear. Animal studies have suggested that choline deficiency might be causally related to carcinogenesis. In addition, several epidemiologic studies have suggested a relationship between folate intake and breast cancer incidence. Polymorphisms of genes regulating one-carbon metabolism have also been implicated in breast cancer risk. In the Long Island Breast Cancer Study Project (LIBCSP), researchers observed an inverse relationship between breast cancer risk and vitamin B intake and noted an independent association between a polymorphism of an important one-carbon-metabolizing gene and breast cancer risk. Because the dietary methyl donors (folate, methionine, choline, and betaine) are closely interrelated in several metabolic pathways, it is important to take each into account when examining potential associations between these micronutrients and carcinogenesis.

To clarify the relationship between methionine, choline, betaine, and breast cancer risk, researchers reviewed data from the LIBCSP, a population-based case-control study of women between the ages of 20 and 98 years living in Long Island, New York. Cases (*n*=1,508) were women with newly diagnosed breast cancer. Controls (*n*=1,556) were age-matched women residing in the same counties with no history of breast cancer. Participants completed a questionnaire assessing known and suspected risk factors for breast cancer, including cigarette smoking, exposure to cigarette smoke, lifetime alcohol use, menstrual and reproductive history, use of hormone replacement therapy, body size, lifetime participation in recreational activities, medical history, and family history of breast cancer. The women also completed a food frequency questionnaire to evaluate habitual food intake over the previous year. The US Department of Agriculture's database was used to assess choline, methionine, and betaine intake. A majority of the participants donated blood samples for genotyping.

On average, these women consumed 326 mg choline, 1.01 g methionine, and 138 mg betaine per day. While methionine and betaine intakes were not related to breast cancer risk in this study, researchers did observe an inverse association between breast cancer risk and choline intake among women in the highest quintile of choline consumption (OR: 0.76; 95% CI: 0.58-1.00) compared with the lowest quintile.

Two single nucleotide polymorphisms (SNPs) of choline-metabolizing genes were independently associated with breast cancer risk in this analysis. PEMT -774G>C (rs12325817) and CHDH +432G>T (rs12676) were both associated with increased breast cancer risk. When compared with the GG genotype, the CC genotype resulted in an OR of 1.30 (95% CI: 1.01-1.67). Compared with the GG genotype, the risk of breast cancer was increased by 19% in women who carried the T allele (95% CI: 1.00-1.41). After separate analysis, however, risk was increased only for those in the GT heterozygous group. When the genetic polymorphisms were evaluated for potential interaction with choline, methionine, and betaine intake, researchers observed a two-fold increase in breast cancer risk in women with the PEMT rs7946 variant genotype who had the lowest betaine intakes (OR 1.90; 95% CI: 1.14-3.16).

In this study, researchers observed a 24% reduction in breast cancer risk among women with the highest intakes of dietary choline and a 30% increase among women homozygous for the minor allele of a gene involved with choline metabolism (PEMT rs12325817). These findings suggest that choline intake is potentially important in reducing breast cancer risk and in curbing the incidence of this common malignancy. Although the estimated adequate intake of choline for adult males is 550 mg/day and for females is 425 mg/day, recent epidemiological studies have shown that women are not meeting this recommendation. The Nurses' Health Study and the European Prospective Investigation into Cancer and Nutrition (EPIC) study showed median intakes to be 323 mg and 300 mg/day, respectively. Further research is needed to determine whether increased intakes of choline might reduce breast cancer risk in the population at large. ■

Xu X, Gammon MD, Zeisel SH, et al. Choline metabolism and risk of breast cancer in a population-based study. *FASEB J.* 2008 Jun;22(6):2045-52. Epub 2008 Jan 29.

EDITORIAL

No Diet for Older, Overweight, Inactive, Hypertensive and Hypercholesterolemic Men Who Smoke and Drink

A study published in the April 2008 issue of *The American Journal of Clinical Nutrition*[1] suggests an association between high egg consumption and all-cause mortality in male physicians. The researchers did note that there was no relationship between egg consumption and cardiovascular disease risk, as has been shown in a number of previous studies. So what did eggs do? Since total mortality was the only endpoint referenced, we just don't know. One should note that the men who ate the most eggs were older, fatter, less likely to exercise, more likely to have diabetes, hypertension, and hypercholesterolemia, more likely to have a parental history of coronary artery disease, and more likely to smoke and drink alcohol—all factors that can affect one's risk of death. But the authors did title their paper "Egg consumption in relation to cardiovascular disease and mortality: the Physicians' Health Study."

As noted in an accompanying editorial by Dr. Robert Eckel, co-chair of the Committee on Cardiovascular and Metabolic Diseases, "The study suffers from the lack of detailed dietary information that may confound the interpretation, such as patterns of dietary intake of saturated fat and *trans*-fats."[2] This is a significant point, given that one might think that doctors who are fatter, more likely to drink alcohol, smoke, less likely to exercise and exhibit hypertension, hypercholesterolemia and diabetes might eat their eggs with foods high in saturated fat (a finding reported nine years ago in the Health Professionals' Follow-Up Study by Hu et al.)[3]

The investigators reported that among male physicians with diabetes, any egg consumption was associated with a greater risk of all-cause mortality; however, the researchers did not comment on the level of diabetes control of the subjects. Poor diabetic control is associated with an increased risk of a number of chronic diseases that also affect mortality. Once again, those who are fatter, and who are more likely to drink alcohol, smoke and less likely to exercise might also be the ones with the poorest diabetes control. No data on A1C levels were available.

So let me suggest that every older, male, overweight, inactive, smoking and drinking, hypertensive, hypercholesterolemic and diabetic doctor who doesn't know how to take care of himself eat only six eggs a week until he gets his act together and maybe gets in better shape. Stop smoking! Control your blood pressure and your LDL:HDL ratio. A little exercise would probably be a good idea. Lose the love handles. If you are diabetic, get your diabetes under control and your A1C levels below 7%. If you don't change these factors you've got more to worry about than how many eggs you eat in a week.

On the other hand, if you're healthy, this study says eggs have no effect on heart disease or stroke risk and you can include them in your diet. When you do, you'll get choline (an underappreciated nutrient that's probably inadequate in your diet), high quality protein, and a spectrum of essential and functional nutrients. What's more, you'll experience greater satiety after a meal including eggs (and consequently, less propensity to snack later on or to compensate with more calories at the next meal).The evidence just keeps getting clearer; an egg a day (or 7-10 a week) is not a factor in heart disease. On the other hand, there is evidence suggesting that an egg a day can help lower the risk of age-related macular degeneration and cataracts, slow the rate of sarcopenia in the elderly, address the choline inadequacy in the general population, and help maintain a healthy body weight. ■

1. Djoussé L and Gaziano JM. Egg consumption in relation to cardiovascular disease and mortality: the Physicians' Health Study. *Am J Clin Nutr*. 2008;87;964-9.

2. Eckel R. Egg consumption in relation to cardiovascular disease and mortality: the story gets more complex. *Am J Clin Nutr*. 2008;87:799-800.

3. Hu et al. A prospective study of egg consumption and risk of cardiovascular disease in men and women. *JAMA*. 1999;281:1387-1394.

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For more commentary on this and other current issues in nutrition, visit Dr. McNamara's blog at www.unscramblingthescience.com